**REMARKS/ARGUMENTS**

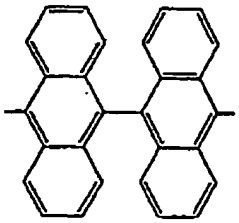
Claims 1-13 are rejected under 35 USC 112. To avoid rejections referring to terminology, claims 1, 2, 8 and 13 are amended to clarify the intended scope of the claims.

As to the rejection that the scope of the compounds is not clear in view of Examples B-11 and B-22, applicants studied these compounds and agree that B-22 be canceled (as set forth above).

However, with regard to compound B-11, in which binaphthyl group and naphthyl group correspond to $Ar_{41}$ and $Ar_{42}$, respectively this comes within the formula B1 when one considers that adjacent substituents attached to an imidazole ring are condensed with each other to form a benzene ring. Withdrawal of the formal rejections is requested.

Claims 1 and 13 are rejected as being anticipated by Inoue. The Examiner states that Inoue's Compound No. VII-21 is a compound of formula B1 in which each of $L_{11}$ and $L_{12}$, is =N-, $L_{13}$ is -O-, each of $Ar_{41}$ and $Ar_{42}$ is an aryl group, and one of $Ar_{41}$ and $Ar_{42}$ comprises a biaryl group having a bond capable of giving an internal rotational isomerism (specifically, comprising the biaryl group represented by the sixth formula on page 25 of the specification). Thus, the Examiner seems to consider that

9,9'-bianthracene-10, 10'-diyl group of the compound No. VII-21, is as below and asserts that this group corresponds to a biaryl group having a bond capable of giving an internal rotational isomerism, as claimed in the invention.

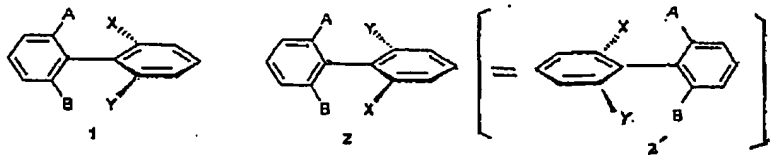


However, the Examiner's position is not correct, based on the, following reason.

As is known in the art, an internal rotational isomerism, which is also called atropisomerism (see, present specification page 24, second paragraph), is a type of stereoisomerism that may arise in systems where free rotation about a single covalent bond is impeded sufficiently so as to allow different stereoisomers (enatiomers) to be isolated. Enclosed is a copy of relevant portion of a reference including general teaching with respect to the atropisomerism (Chem. Soc. Rev., 2001, 30, 145, 147 and 157).

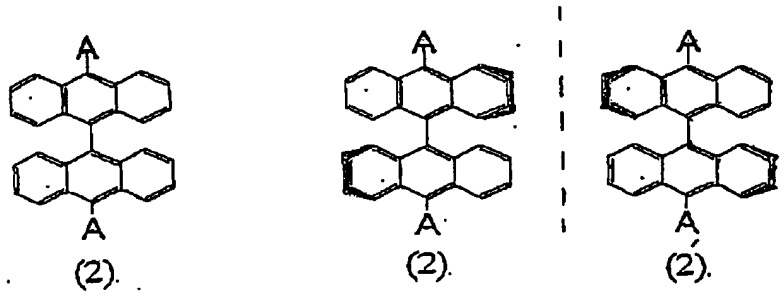
As detailed therein, for example, twisted biphenyls 1 and 2 (page 146) are enantiomers as consequence of each having a chirality (or dissymmery) axis. Herein, "enantiomers" is

molecules that are mirror images of one another (i.e., nonsuperimposable mirror images). For example, biphenyl 2 can also be represented by 2', as illustrated below. Apparently, 2' is a mirror image of 1.



Thus, biphenyls 1 and 2 are atropisomers (or internal rotational isomers) and such a biphenyl is also said to be a biaryl having a bond capable of giving an internal rotational isomerism.

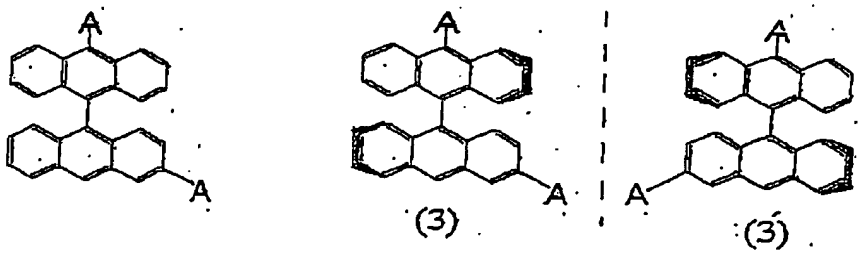
Turning to Compound No. VII-21 of Inoue, this compound is represented simply by formula (2), as below:



wherein A is a residue attached to 9,9'-bianthracene-10.10'-diyl, that is, 4-(2-phenyl-1,3,4-oxadiazolyl)-phenyl.

Conformation of the compound is also represented by (2') or its mirror image (2"). As can be seen therefrom, (2') and its mirror image (2") are superimposable and therefore is identical in conformation, that is, enantiomerism is impossible in this compound. Accordingly, 9,9'-bianthracene-10.10'-diyl included in Inoue's compound VII-21 is not a biaryl group having a bond capable of giving an internal rotational isomerism (atropisomerism).

On the contrary, for example, the compound of formula (3) is represented by conformation (3') or its mirror image (3"), as below. As can be seen, (3') and (3") are nonsuperimposable and are enantiomers. Thus, the compound of formula (3) arises atropisomerism and it is concluded that the compound of formula (3) includes a biaryl group having a bond capable of giving an internal rotational isomerism.




(3) (3')

Based on the foregoing, Compound VII-21 of Inoue does not fall within the scope of the claimed formula B1. Thus, neither compound falling within scope of the claimed formula B1 nor biaryl group having a bond capable of giving the internal rotation isomerism is taught or suggested in Inoue. It is therefore submitted that claims 1 and 13 are not anticipated by or obvious over Inoue.

The remaining claims are rejected over various combinations of Inoue with other documents. However, in each rejection Inoue is cited with respect to its disclosure of compound No. VII-21. As discussed in detail above, the compound of Inoue on which the Examiner relies is not within the present claims. Nor is there any suggestion to modify the compound to come within the present claims. The compound of Inoue, in particular, does not have a biaryl group having a bond capable of giving an internal rotational isomerism as explained in detail above. The art combined with Inoue does not supply this deficiency or missing teaching. Therefore, the various obviousness rejections relying on Inoue in combination with other art, does not render the present invention obvious.

In view of the above, it is submitted that the present invention is not shown or suggested by the cited art. Withdrawal of the rejections and allowance of the application are respectfully requested.

Respectfully submitted,

Frishauf, Holtz, Goodman
& Chick, P.C.
220 Fifth Ave., 16th Floor
New York, NY 10001-7708
Tel. No. (212) 319-4900
Fax No.: (212) 319-5101
MJC/ld

MARSHALL J. CHICK
Reg. No. 26,853

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# Atropisomerism, biphenyls and the Suzuki coupling: peptide antibiotics†

**Paul Lloyd-Williams and Ernest Giralt**

*Department of Organic Chemistry, Universitat de Barcelona, Martí i Franquès, 1-11, 08028 Barcelona, Spain*

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**The formidable synthetic challenge posed by the vancomycin class of glycopeptide antibiotics has only recently been met. Foremost among the difficulties associated with the synthesis of these molecules is the control of non-conventional stereochemical issues. These are a consequence of the molecules possessing biphenyl and biaryl ether linkages between amino acid residues situated within the constituent macrocycles. Among the keys to success is the availability of methods that allow the efficient formation of biaryl linkages between amino acid derivatives under mild conditions. Recent progress in the chemistry of the Suzuki coupling suggests that this constitutes a very powerful and general method for the synthesis of peptide biphenyls.**

## 1 Atropisomerism

Atropisomerism is a type of stereoisomerism that may arise in systems where free rotation about a single covalent bond is impeded sufficiently so as to allow different stereoisomers to be isolated.[1] It is manifested typically in *ortho*-substituted biphenyls (or, more generally, biaryls) where steric congestion between the substituents restricts free rotation about the $sp^2$–$sp^2$ carbon–carbon bond.

Biphenyls **1** and **2** are enantiomers as a consequence of each having a chirality axis with a defined sense of chirality. (In this review we use *chirality axis* and *chirality plane* following the latest IUPAC guidelines.[1] We note, however, that these terms are not completely free from controversy and for a critical discussion and alternative proposals we refer interested readers to the article by Mislow[2]).

The configuration of a molecule having a chirality axis may be specified as *R* or *S* by application of the Cahn–Ingold–Prelog priority rules. The descriptors *aR* and *aS* are sometimes used to distinguish axial chirality from other types but the use of a prefix is optional. Alternatively such molecules may be treated as helices and assigned *M* or *P* stereochemistry. For compounds with chirality axes, the descriptions *aR* and *M* and those of *aS* and *P* correspond.

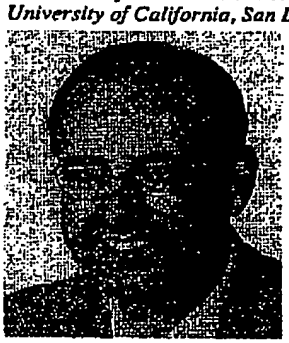
Atropisomerism in biaryls has been quite extensively studied and a considerable amount of data for various different systems has been reported.[3–5] The majority of tetra-*ortho* substituted biphenyls present a barrier to rotation about the single $sp^2$–$sp^2$ bond that is sufficiently high to prevent the interconversion (or racemization) of atropisomers at room temperature and often above. Consequently, the different atropisomers in tetra-substituted biphenyls can usually be resolved. Atropisomer stability is, however, considerably reduced when two or more of the substituents are small. Atropisomeric tri-*ortho* substituted

† Abbreviations: Bn = benzyl; Boc = *tert*-butoxycarbonyl; dba = dibenzylideneacetone; Ddm = 4,4′-dimethoxydiphenylmethyl; DMSO = dimethylsulfoxide; FDPP = pentafluorophenyl diphenylphosphinate; MEM = methoxyethoxymethyl; Ms = methylsulfonyl; Piv = pivaloyl; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; Tfa = trifluoroacetyl; TFA = trifluoroacetic acid; Z = benzoxycarbonyl.

*Paul Lloyd-Williams received his BSc in 1978 and his PhD in 1985 from the University of Manchester, UK. After postdoctoral work at the University of Arizona, USA, on the total synthesis of biologically active natural products, he joined Professor Ernest Giralt's group at the Universitat de Barcelona in 1988, working on peptide synthesis methods and the total synthesis of marine natural products. He is currently Associate Professor of Chemistry at the Universitat de Barcelona.*

**Paul Lloyd-Williams**

*Ernest Giralt received his first degree in 1970 and his PhD in 1974 from the Universitat de Barcelona. After postdoctoral work at the Université de Montpellier, France, he returned as Assistant Professor. He was subsequently promoted to Associate Professor in 1977 and to Full Professor in 1986. He was Visiting Professor at the University of California, San Diego and Research Associate at the Scripps Research Institute, USA, in 1991. Professor Giralt's main research interests lie in the fields of molecular recognition, peptide synthesis and structure determination, in particular using nuclear magnetic resonance spectroscopy. He was one of the founding members of the European Peptide Society and received the Narcis Monturiol prize in 1992 and the Leonidas Zervas award in 1994.*



**Ernest Giralt**

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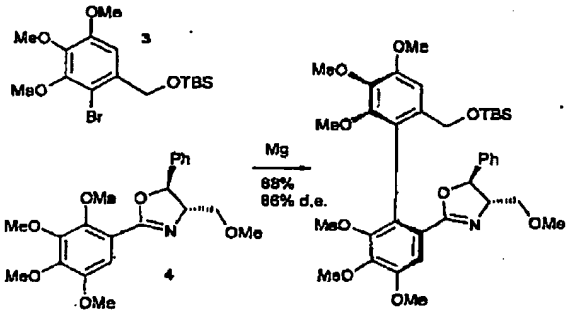
atropisomer selectivity in biaryl couplings.[10,19] Studies in this field, of course, benefit from the enormous pre-existing body of work on stereocontrol in organic synthesis. Although this has generally concerned itself with the control of stereochemistry when the stereogenic unit is a carbon atom, the principles involved are applicable to systems where the stereogenic unit is an axis.

Important results have been achieved in both inter- and intramolecular couplings but general methods that allow the reliable atropisomer-selective (atrop-selective) synthesis of biaryls are still some way from being a reality.

### 3.1 Atrop-selective intermolecular couplings

In intermolecular atrop-selective couplings, high diastereomeric excesses have been obtained using chiral oxazolines. Good results are, however, usually only obtained with aromatic compounds in which the *ortho* substituents next to the coupling position are very different in size, for example when one is a hydrogen atom and the other an alkyl group. The method, consequently, works well for the synthesis of biaryls bearing three *ortho* substituents. These present a barrier to rotation that is lower than that in tetra-*ortho* substituted biaryls and although they can often be resolved, racemization-free removal of the chiral auxiliary is frequently not possible. (Scheme 3.)



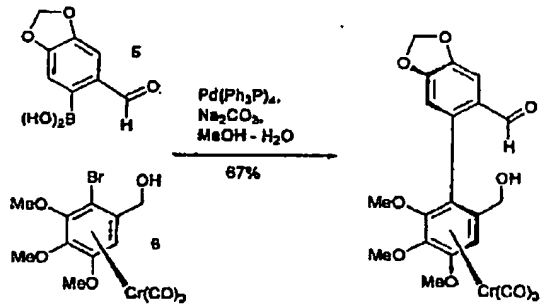

Scheme 3

The enantiomer of the natural product schizandrin was prepared by atrop-diastereoselective crossed biaryl coupling using an oxazoline substituent as chiral auxiliary.[20] In this particular case a tetra-*ortho*-substituted biphenyl was obtained in diastereomeric excess of 86% after coupling between aryl bromide 3 and oxazoline 4.

Another natural product, steganone, has been synthesized using an atrop-selective[21] Suzuki coupling between the achiral boronic acid 5 and the chiral arenechromium complex 6. The coupling between 5 and 6 proceeded in good yield to give the desired (*R*) [or (*M*)]-atropisomer, the other not being detected in the worked-up product. (Scheme 4.)

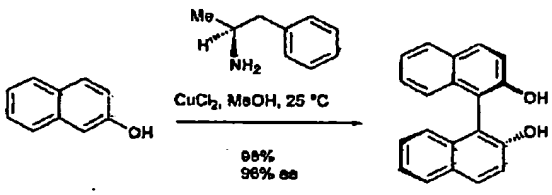
The use of aryl reactants incorporating a chiral auxiliary as a control element for inducing atropisomer selectivity can, however, be limited by their commercial availability as well as by limitation to a particular biaryl substitution pattern. Stereoselective aryl couplings have also been reported using aromatic systems that themselves do not incorporate chiral control elements through the use of chiral catalysts or reagents.

One example is the atrop-enantioselective coupling of 2-naphthol to give the corresponding binaphthol, which can be achieved in good chemical yield and high optical purity



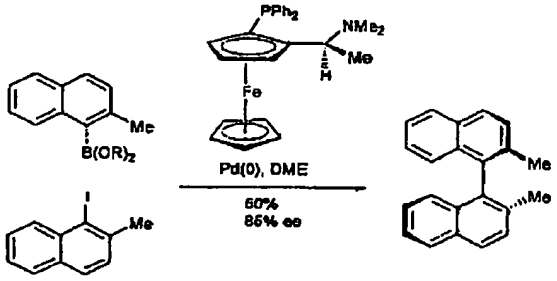

Scheme 4

(96% ee) by chiral copper-complex-mediated phenolic oxidation, although large quantities (up to a 16 fold excess) of the chiral reagent are required. (Scheme 5.)




Scheme 5

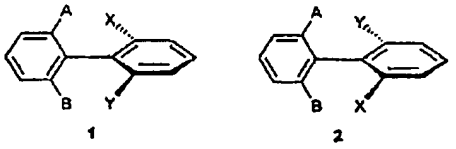
Promising results have also been achieved with palladium(0) complexes in the presence of chiral ligands, as the atrop-enantioselective Suzuki reaction below illustrates.[22] Chiral binaphthalene derivatives in up to 85% ee can be formed by careful choice of the ligand. (Scheme 6.)




Scheme 6

### 3.2 Atrop-selective intramolecular couplings

Making a given biaryl coupling intramolecular can bring with it several benefits. Not only may the bridge linking the aromatic rings lead to an improvement in the yield and regioselectivity of the coupling reaction, but it may also influence the barrier to atropisomerization and be the site of chirality from which any asymmetric induction emanates. After coupling, there are several possibilities for the subsequent treatment of bridges: all



1 2

biphenyls can often be interconverted above room temperature. Di-*ortho* substituted biphenyls can usually only be resolved if both of the substituents are large.

Whatever the substitution pattern, in solution the aromatic rings in biphenyls are usually neither coplanar nor perpendicular in their lowest energy conformations.[5] The steric requirements of *ortho*-substituents tend to enforce non-coplanarity but the stabilization of the biphenyl system by $\pi$-electron overlap is greatest when the rings are coplanar. These effects tend to pull in opposite directions and the inter-ring torsion angle is usually between 42° and 90°. In the crystal, however, some biphenyls including biphenyl itself are planar.[6]

Atropisomerism is not restricted to biaryls. Within systems having the $sp^2$–$sp^2$ single bond type, it may also be manifested in sterically impeded substituted styrenes and in certain aromatic amides and anilides.[7–9] Cases of atropisomerism about single $sp^2$–$sp^3$ carbon–carbon bonds are known and, more unusually, some highly sterically hindered $sp^3$–$sp^3$ single bonds also exhibit degrees of restricted free rotation that permit stereoisomers to be resolved. Complex molecular architectures such as those of the vancomycin group of antibiotics present nonconventional stereochemical issues that originate in the restricted rotation of substituted aromatic rings within macrocyclic structures. The practitioners of the first total syntheses of these molecules have considered these stereochemical phenomena to be cases of atropisomerism. We follow this usage in this review (see Section 4).

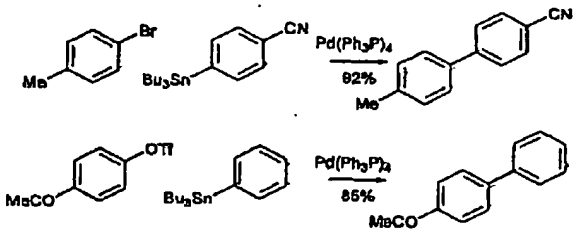
## 2 Biaryls and their synthesis

The biaryl[10–13] sub-unit is found in a wide variety of natural products, including alkaloids, coumarins, flavonoids, lignans, polyketides, tannins, terpenes and peptides. Compounds incorporating biaryl building-blocks also find application as chiral reagents, chiral phases for chromatography and chiral liquid crystals to name only the most important. Their ubiquity makes biaryl compounds important synthetic targets and many methods for their chemical synthesis have been described.[10–12] The key step is almost always bond formation (often referred to as coupling) between the two aromatic portions of the molecule.

The synthetic problem is simplified in those cases where both aromatic rings are identical and the product is a symmetrical biaryl. Although methods for the formation of unsymmetrical biaryls have been known for decades it is only relatively recently, with the advent of palladium(0)-based coupling reactions, that versatile procedures for their formation under relatively mild conditions have become available.[12] Without doubt it is those methods based on aryltin and especially arylboron reagents that have seen the most important advances. Palladium(0) catalyzed crossed coupling reactions using these reagents have now become among the most important carbon–carbon bond-forming reactions available to the organic chemist. They can be applied in a variety of circumstances for the synthesis of biaryls and a range of other types of product and tolerate a much wider range of functionality and structural diversity than other alternatives.

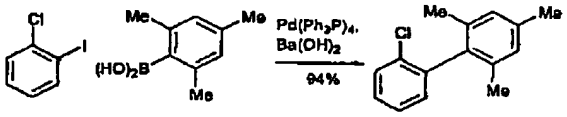
Mechanistically these reactions are complex and much studied.[12,14,15] In general terms they are thought to proceed *via* oxidative addition of the catalyst to the aryl halide, followed by a transmetallation step that gives a diaryl palladium species. Reductive elimination from this then gives the biaryl compound and regenerates palladium(0) which can re-enter the catalytic cycle.

Arylstannanes can be induced to react with aryl halides or aryl triflates through the agency of Pd(0) catalysis to give biaryls, a reaction known as the Stille coupling.[16] The possibility of using aryl triflates adds extra versatility to the method since it allows phenols to serve as substrates for the synthesis of biphenyls. (Scheme 1.)



Scheme 1

A similar but even more extensively used method employs arylboronic acids or their derivatives instead of aryltin compounds and aryl halides as the second component in a reaction known as the Suzuki coupling,[15,17,18] which has become one of the most widespread methods for the synthesis of biaryls. (Scheme 2.)



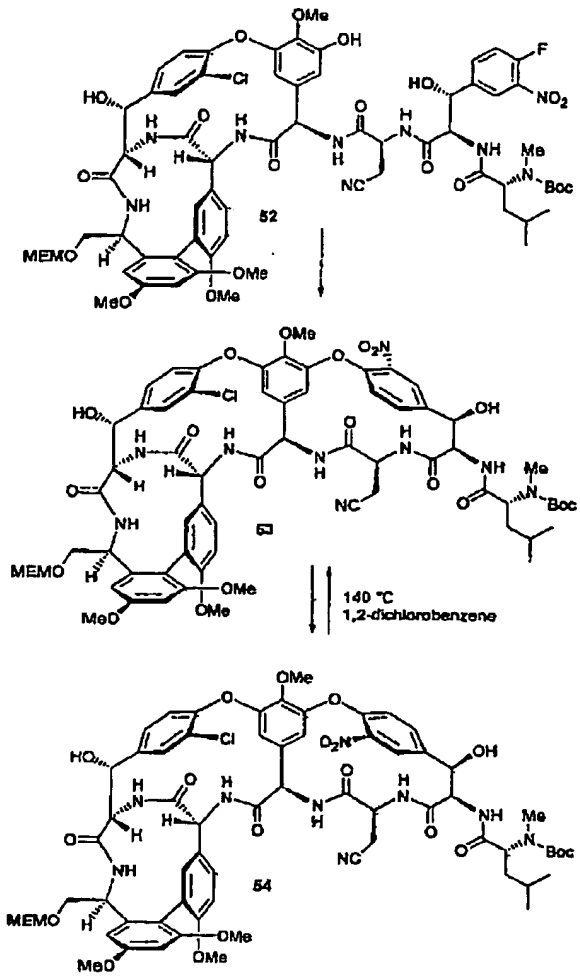
Scheme 2

Among the most important virtues of the Suzuki coupling may be counted its tolerance to a wide variety of functional groups and the comparative ease with which arylboronic acids and their derivatives may be prepared. The relative stability of these reagents to water and to oxygen also contributes notably to the operational simplicity of the method. A further important advantage of the Suzuki coupling is its often good performance when couplings involving sterically crowded aromatic rings are involved.

For both symmetrical and unsymmetrical biaryls, questions of regioselectivity (whether or not the coupling reaction can be brought about at the correct carbon atom of each of the aromatic rings) and stereoselectivity (whether or not the coupling can be influenced to produce a given atropisomer of the biaryl preferentially) may arise. In certain cases efficient stereoselective (atrop-diastereoselective and even atrop-enantioselective) synthesis of biaryls can now be achieved.

## 3 Stereocontrol in biaryl synthesis

Since continuing advances in chemical methods for the formation of the carbon–carbon bond in biaryls are making their synthesis more and more routine, attention has focused increasingly on the problem of how to achieve efficient




Scheme 23

## 6 Acknowledgements

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